REMARKS/ARGUMENTS

The Objection to the Specification Should Be Withdrawn

The specification has been objected to for containing an embedded hyperlink and/or other form of browser executable code. The Office Action indicates on page 2 that "[t]here are two links one each in paragraph 29 and paragraph 69 of the instant specification."

Applicants have reviewed paragraphs 29 and 69 of the instant specification and are unable to find an embedded hyperlink and/or other form of browser executable code in either of these paragraphs. Possibly, the Examiner intended to refer one or more other paragraphs in the instant specification. However, Applicants respectfully request that the Examiner identify the "links" in paragraphs 29 and 69 in the next non-final Office Action or withdraw this objection.

Upon review of the instant specification, Applicants identified a single occurrence of an embedded hyperlink and/or other form of browser executable code in paragraph 89. In interest of expediting prosecution of the instant application, Applicants have amended paragraph 89 of the specification to delete the recitation of "http://" that occurs immediately before the recitation of "www.neb.com/neb/inteins.html". The amendment of the specification is purely formal in nature and thus, does not introduce new matter.

Status of the claims

The Office Action indicates that claims 1-6, 9-14, 17-19, 23, and 25-31 are rejected and that claims 7, 8, 15, 16, 20-22, 24, and 32-34 are withdrawn from consideration for being drawn to non-elected subject matter.

Applicants have cancelled 7, 8, 15, 16, 20-22, 24, and 32-34 without prejudice or disclaimer and expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the subject matter of these non-elected claims.

Applicants have additionally cancelled claims 6, 9, 10, 19, and 28 without prejudice or disclaimer in the interest of expediting prosecution of the instant application.

Applicants have amended claims 1, 2, 11-13, 17, 23, 25-27, and 29-31 as described in detail below.

Applicants have amended claim 1 to incorporate certain limitations of claims 6-8 into part (ii) of claim 1. In addition, Applicants have further amended part (b) of claim 1 to add certain limitations of claims 9 and 10, and part (i) to add certain limitations of claims 19-22. Finally, Applicants have amended claim 1 to indicate that the multi-cellular organism is a plant. Applicants have amended claim 27 in a like manner. Support for the amendments to claims 1 and 27 can be found in original claims 1, 6-8, 9, 10, 19-22, 26, and 28, and in the specification, particularly in the paragraph bridging pages 20-21.

Applicants have amended dependent claims 2, 11, 17, 23, 25, 26, 29-31 to add --plant-- immediately before each occurrence of the term "organism" for the sake of consistency with amended, independent claims 1 and 27.

Finally, Applicants have amended claims 11-13 to change claim dependency to claim 1 following the cancellation of claims 9 and 10. In addition, claims 11-13 were further amended to maintain proper antecedent basis for the terms used therein. The amendments to claims 11-13 are fully supported by the original claims and specification. Particular support for these amendments is the same as discussed above for the amendment of claim 1.

Applicants expressly reserve the right to file continuing applications or take such other appropriate measures deemed necessary to protect the subject matter of their original claims and disclosure.

No new matter has been added by way of amendment of the claims.

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 are pending.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Rejections of the Claims Under 35 U.S.C. § 101 Should Be Withdrawn

Claims 1-6, 9-14, 17-19, 23, 25, 27, and 29-31 have been rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Claims 6, 9, 10, and 19 have been cancelled. Claims 1, 2, 11-13, 17, 23, 25, 27, and 29-31 have been amended. This rejection is respectfully traversed.

The Office Action indicates that because claims 1-6, 9-14, 17-19, 23, 25, 27, and 29-31 are directed to a method of controlling a genetically modified organism or part thereof, these claims encompass humans and are not patentable.

Applicants have amended independent claims 1 and 27 to recite that the multi-cellular organism is a plant. As amended, claims 1 and 27 and their respective dependent claims are not directed to non-statutory subject matter.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 101 should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 1-6, 9-14, 17-19, 23, and 25-31 have been rejected under 35 U.S.C. § 112, first paragraph. Claims 6, 9, 10, 19, and 28 have been cancelled. Claims 1, 2, 11-13, 17, 23, 25-27, and 29-31 have been amended. This rejection is respectfully traversed.

Enablement

Claims 1-6, 9-14, 17-19, 23, and 25-31 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

The Office Action acknowledges that the specification provides guidance for the transformation of *Nicotiana* plants with provectors comprising the NPTII gene, the 5' end of TMV, a movement protein and a viral coat protein, and the introduction of integrase using the VirE2 protein system for translocation of the polypeptide into the cell.

The Office Action alleges, however, that the specification does not provide guidance for translocation of polypeptides into the cell using any other system or for any other genes functioning as predicted other than NPTII, GUS, and the Green Fluorescent Protein. The Office Action asserts that the translocation and interaction of polypeptide fragments of genes is unpredictable, citing Mackenzie ((2005) *Trends Cell Biol.* 15:548-554) in support of this position. The Office Action concludes that given the unpredictability in the art at the time of Applicants' invention and the lack of guidance in the specification, undue experimentation would be required for one of skill in the art to practice Applicants' invention as claimed.

Applicants respectfully disagree with the position of the Office Action that the specification does not reasonably provide enablement for the pending claims. In the interest of expediting prosecution of the instant application, Applicants have amended the claims 1 and 27.

Amended claim 1 defines that the multi-cellular organism is plant or part thereof, that the plant or part thereof contains a heterologous nucleic acid encoding a protein and that causing the expression of the protein from the heterologous nucleic acid involves delivering a polypeptide to the multi-cellular plant organism or part thereof, said polypeptide rendering said heterologous nucleic acid expressible, said polypeptide being selected from the group consisting of a site-specific recombinase, a flippase, a resolvase, an integrase, a polymerase, a transposase and a transcription factor. Furthermore, the protein is specified as: containing a protein portion

enabling leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein said protein portion is a domain of a viral movement protein, a domain of a viral coat protein, a domain of a plant or animal transcription factor capable of cell-to-cell or systemic movement, a domain of a plant or animal peptide intercellular messenger, or an artificial peptide capable of enabling cell-to-cell movement; being capable of causing expression of said protein in cells containing said heterologous nucleic acid by a DNA or RNA modifying activity of a segment of said protein, said segment being selected from the group consisting of a site-specific recombinase, a flippase, a resolvase, an integrase, a polymerase, and a transposase, or said protein has a segment being a transcription factor inducing transcription of said heterologous nucleic acid; and optionally being capable of controlling a cellular process of interest.

Similarly, amended claim 27 defines that the multi-cellular organism is plant or part thereof; that the protein contains a protein portion enabling said protein of leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein said protein portion is a domain of a viral movement protein, a domain of a viral coat protein, a domain of a plant or animal transcription factor capable of cell-to-cell or systemic movement, or a domain of a plant or animal peptide intercellular messenger; that the protein has a segment having a DNA or RNA modifying activity, said segment being selected from the group consisting of a site-specific recombinase, a flippase, a resolvase, an integrase, a polymerase, and a transposase, whereby said protein is capable of controlling expression of said protein in cells containing said heterologous nucleic acid, or said protein has a segment being a transcription factor inducing transcription of said heterologous nucleic acid; and that the heterologous nucleic acid optionally adapted for controlling a cellular process of interest.

In contrast to the view of the Office Action, Applicants' specification provides sufficient guidance for one of skill in the art to make and use their claimed invention including, for example, proteins of interest other than NPTII, GUS, and GFP. The NPTII, GUS, and GFP proteins are proteins of interest used in the invention as examples of proteins expression of which may be controlled by the invention. These three proteins constitute a diverse group of proteins that are unrelated. Many other proteins can be expressed in plants, cf. the cited prior art

references, and there is no reason to assume that only NPTII, GUS and GFP can be expressed by the method of the invention.

Example 1 does not use pro-vectors or the 5' end of TMV but non-viral vectors. Therefore, the invention does not only provide guidance for the use of the 5' end of TMV as alleged in the Office Action.

In Examples 1 and 3, a recombinase and an integrase, respectively, were provided to plant cells using particle bombardment using a construct encoding cre and integrase, respectively, under the control of the Arabidopsis actin2 promoter (cf. page 36, bottom; page 39 bottom). Thus, systems other than the VirE2 protein system for translocation are not only generally described in the specification but also used in the Examples.

Mackenzie relates to targeting of nuclear-encoded proteins to cellular organelles such as mitochondria, plastids or the peroxisome. In the invention, targeting to these organelles is not required. It is only necessary that the polypeptide can interact with the heterologous nucleic acid present in cells of the plant. Examples 1 to 3 of the present invention as well as Hooykaas *et al.* (WO 01/89283) show that interaction of the introduced polypeptide with a heterologous nucleic acid works. There is therefore no reason to assume that there is unpredictability to such an extent that the process of the invention is not enabled.

Moreover, in the method of claim 1, an amplification effect is achieved by the function of part (i) of claim 1 by spreading of the protein within the plant after its formation. Therefore, in the invention, the cellular process of interest can be triggered even if the likelihood of an interaction of the external signal with the heterologous nucleic acid is unpredictable or low.

In view of the amendments and above remarks, it is apparent that those of skill in the art would be able to practice the present claims without undue experimentation. Accordingly, the enablement rejection of the claims should be withdrawn.

Written Description

Claims 1-6, 9-14, 17-19, 23, and 25-31 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

The Office Action alleges that the claims are broadly drawn to multitudes of sequences that contain unspecified fragments of polypeptide sequences and unspecified length and activities of the polypeptides for use in a method of controlling genetically modified plant and plants therefrom but that the specification only describes the NPTII gene, the 5' end of TMV, a movement protein and a viral coat protein, and the introduction of integrase using the VirE2 protein system for translocation of the polypeptide into the cell. The Office Action further alleges that the specification does not describe any other systems or gene sequences for use in the methods of the claimed invention. The Office Action concludes that the specification fails to provide an adequate written description of the claimed genus of sequences and furthermore, that any method of using them, and the resulting products, would also be inadequate described. The Office Action cites *Regents of the University of California v. Eli Lilly and Co.*, 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997) and *Amgen v. Chugai*, 18 USPQ2d 1016 (Fed. Cir. 1991) in support of this conclusion.

The Examiner appears to have misunderstood the claims. On page 5 at lines 3-6 of the Office Action, the Examiner states that "[t]he claims are broadly drawn to multitudes of sequences that contain *unspecified fragments* of polypeptides sequences . . . ." (emphasis added). The claims, however, are not drawn to fragments. Therefore, Applicants respectfully request that the Examiner reconsider this rejection after properly construing the claims.

While Applicants respectfully disagree with this position of the Office Action that the specification does not provide an adequate written description of their claimed invention, Applicants have amended Applicants have amended claims 1 and 27 as described above in the interest of expediting the prosecution of the instant application.

The specification provides an adequate description of the subject matter encompassed by the amended claims to reasonably convey to one skilled in the relevant art that Applicants had possession of the invention at the time of filing. Amended claims 1 and 27 recite a polypeptide that either has a specified enzymatic activity selected from the group consisting of a site-specific recombinase, a flippase, a resolvase, an integrase, a polymerase, a transposase and a transcription factor. No fragments of polypeptides are recited. Amended claims 1 and 27 further recite that the proteins contains a protein portion that is capable of enabling leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein the protein portion is a domain of a viral movement protein, a domain of a viral coat protein, a domain of a plant or animal transcription factor capable of cell-to-cell or systemic movement, a domain of a plant or animal peptide intercellular messenger, or an artificial peptide capable of enabling cell-to-cell movement. Such enzymes, transcription factors, and protein portions enabling cell-to-cell movement were generally known in the art at the time of the invention and are adequately described in the instant specification to reasonably convey to one skilled in the art that, at the time the application was filed, Applicants had possession of the claimed invention. Accordingly, the written description requirement of 35 U.S.C. §112, first paragraph, has been satisfied.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 1, 3, 5-6, 9-14, 17-19, 23, and 25-31 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hooykaas *et al.* (WO 01/89283). Claims 6, 9, 10, 19, and 28 have been cancelled. Claims 1, 11-13, 17, 23, 25-27, and 29-31 have been amended. This rejection is respectfully traversed.

In the last paragraph on page 7 of the Office Action, the Examiner asserts that Hooykaas *et al.* teaches the translocation of the CRE polypeptide into plant cells using the VirE2 and trans-splicing to achieve recombination to induce the transcription of a heterologous gene, NPTII. Curiously, the Examiner provides no further remarks in this section of the Office Action and therefore, fails to provide Applicants with any basis for why he has rejected the claims as being anticipated by Hooykaas *et al.*

Applicants respectfully request that the Examiner either state with particularity in the next non-final Office Action the reasons why he believes that each of claims 1, 3, 5-6, 9-14, 17-19, 23, and 25-31 is anticipated by Hooykaas *et al.* or withdraw this rejection.

Applicants respectfully disagree with the unsupported position of the Office Action that Hooykaas *et al.* anticipates claims 1, 3, 5-6, 9-14, 17-19, 23, and 25-31. Pending claims 1 and 27 and their respective dependent claims are novel over Hooykaas *et al.*, since Hooykaas *et al.* does not disclose a method comprising expression of a protein that is capable of leaving a cell and entering other cells of a multi-cellular organism. Furthermore, the protein expressed by Hooykaas *et al.* (an antibiotic resistance) is not capable of causing expression of said protein in cells from said the heterologous nucleic acid that encodes the protein.

As discussed above, Applicants have amended claims 1 and 27. For the same reasons as discussed above for pending claims 1 and 27, Applicants submit that amended claims 1 and 27 and their respective dependent claims are not anticipated by Hooykaas *et al.*

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 102(b) should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-6, 9-14, 17-19, 23, and 25-31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO

01/89283) and further in view of Xu *et al.* (WO 00/71701). Claims 6, 9, 10, 19, and 28 have been cancelled. Claims 1, 2, 11-13, 17, 25-27, and 29-31 have been amended. This rejection is respectfully traversed.

The Office Action asserts that Klimyuk *et al.* teaches a method for expressing a nucleic acid sequence of interest in plants providing at least two precursor vectors wherein the processing of the precursor RNA is by RNA splicing, ligation and recombination, wherein the cell provides in trans functions necessary for replicon replication, virus particle assembly, wherein the process results in the expression of multiple genes of a biochemical pathway or cascade wherein the heterologous sequence is integrated stably into a host chromosome, and wherein the heterologous nucleic acid introduced is a vector comprising TMV, a viral movement protein and the introduction of CRE into the cell, when jointly present with the LOX sites, commences RNA production from the amplicon. The Office Action further asserts that Hooykaas *et al.* teaches the translocation of the CRE polypeptide into plant cells using the VirE2 and trans-splicing to achieve recombination to induce the transcription of a heterologous gene, NPTII, and that Xu *et al.* teaches the use of the intein-mediated system for trans-splicing a first polypeptide fragment with a second polypeptide to achieve gene function.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art to modify the method taught by Klimyuk *et al.* by using the system taught by Klimyuk *et al.* to translocate recombinase into the cells as taught by Hooykaas *et al.* and suggested by Klimyuk *et al.* that there is a long felt need to improve the safety of plant expression systems. The Office Action asserts that several elements of the claims are well known in the art and considered to be design choices.

Although Applicants respectfully disagree with the position of the Office Action that the cited combination of references renders obvious their claimed invention, Applicants have amended Applicants have amended claims 1 and 27 as described above in the interest of expediting the prosecution of the instant application. Applicants believe amended claims 1 and

27 and their respective dependent claims are not obvious in view of the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.* for the following reasons.

Klimyuk *et al.* does not teach a method comprising expression of a protein from a heterologous nucleic acid, wherein said protein is capable of both

(i) leaving a cell and entering other cells of said multi-cellular organism or a part thereof, and

(ii) causing expression of said protein in cells containing said heterologous nucleic acid.

Further, in Klimyuk *et al.*, the viral movement or coat protein do not have any of the enzymatic activities or the binding activity of a transcription factor as recited in item (ii) of amended claim 1.

Thus, in the present invention, the protein is capable of causing its own expression. The features (i) and (ii) provide the method with the advantage that expression may be induced in only a small number of cells by the external application of a signal that causes the expression of part (b) of claim 1. The expressed protein can then spread to cells that have not been reached by the external signal and cause expression of said protein in such cells. In this way, the externally applied signal is amplified and spread in plant tissue, allowing control of the plant in many more cells or tissues than could be reached by the external signal. Klimyuk *et al.* contains no suggestion to the use of a protein having, at the same time, the functions of features (i) and (ii) above. Instead, Klimyuk *et al.* uses viral vectors that may express a viral movement protein or coat protein that allow movement of the viral vector in plant tissue. The movement or coat protein does not, however, cause its own expression and does not have any of the activities recited in part (ii) of amended claim 1.

Hooykaas *et al.* does not disclose any of features (i) and (ii) above. Hooykaas *et al.* describes translocating a recombinase into plant cells. However, Hooykaas *et al.* does not disclose that the protein expression of which is caused by the recombinase is capable of leaving a cells and entering other cells nor that it can cause expression of the protein. Since the protein

caused to be expressed by Hooykaas *et al.* is a resistance protein, there is no reason to assume that the resistance protein has any of the functions of features (i) and (ii) above.

Xu *et al.* (WO 00/71701) relates to intein trans-splicing. Xu *et al.* is essentially unrelated to the invention and to Klimyuk *et al.* as well as to Hooykaas *et al.* Furthermore, Xu *et al.* does not disclose a method having features (i) and (ii) above. Moreover, Xu *et al.* does not disclose a protein having, in addition to the features (i) and (ii), an activity according to item (ii) of amended claim 1. Therefore, neither Hooykaas *et al.* nor Xu *et al.* can render obvious the invention either alone or in combination with each other and Klimyuk *et al.*

In summary, one of skill in the art would not find that the subject matter encompassed by the amended claims is obvious in view of the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al*. As discussed above, one of skill in the art would not have combined the teachings of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al*. to make Applicant's invention as presently claimed. More importantly, even if the skilled person had combined the teaching of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al*., this combination fails to provide all of the elements of the amended claims. Therefore, the Examiner has failed to raise a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Status of the Claims of Co-Pending Application No. 10/535,766

The pending claims of co-pending Application No. 10/535,766 (371(c) date June 22, 2005) are drawn to a method of controlling a genetically-modified plant or plant cells and plants and compositions used in this method. The method comprises the steps of providing a genetically-modified plant or plant cells, wherein the plant or plant cells contain a heterologous nucleic acid encoding a first polypeptide containing or consisting of a first fragment of a protein,

introducing a second polypeptide into cells of the genetically-modified plant or plant cells, wherein the second polypeptide containing a second fragment of the protein and a peptide sequence enabling the introduction of the second polypeptide into cells of the genetically-modified plant or plant cells, whereby the first fragment and the second fragment jointly generate a predetermined function of the protein only when jointly present. Claims 1-9 and 14-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and for failure to comply with the written description requirement. Claims 1-9 and 14-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701).

Status of the Claims of Co-Pending Application No. 10/535,780

The pending claims of co-pending Application No. 10/535,780 (371(c) date June 22, 2005) are drawn to a method of controlling a controlling a genetically-modified plant and plants and compositions used in this method. The method comprises the steps of providing a genetically-modified plant, whereby cells of said genetically-modified plant contain a heterologous nucleic acid and whereby the genetically-modified plant is inactive with regard to a cellular process of interest, and switching on the cellular process of interest by directly introducing a polypeptide from a cell-free composition into cells containing the heterologous nucleic acid, wherein the polypeptide and said heterologous nucleic acid are mutually adapted such that the polypeptide is capable of switching on the cellular process of interest. Claims 1-4 and 6-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and for failure to comply with the written description requirement. Claims 1, 3, 4, 6-8, 10-17, 23-26, and 29-32 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Hooykaas *et al.* (WO 01/89283). Claims 1-4 and 6-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701).

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§ 101, 102(b), 103(a), and 112, first paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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